REMARKS

I. Halfway down page 2 of the Office Action, claims 4 and 5 were rejected under 35 U.S.C. 112, second paragraph.

The rejection has been overcome and the rejection can be removed.

II. On page 4 of the Office Action, claims 1-2, 6-10, 20 and 21 were rejected under 35 U.S.C. 103(a) over US20030165806 (Pausch) in view of Gaber and further in view of Fairman.

According to the Examiner, Pausch teaches expression of a human potassium channel in a yeast mutant. Gaber was alleged to teach assays for identifying inhibitors or activators of potassium channels expressed in mutant *S. cerevisiae* cells having inactivated endogenous potassium channels of TRK1, or TRK1 and TRK2; and Fairman et al. was alleged to teach a triple mutant of *S. cerevisiae*.

The rejection is traversed for the following reasons.

Pausch relates to a human potassium channel which in the course of experimentation was expressed in a yeast that does not express one endogenous potassium channel.

As stated in the record, Gaber, in the first full paragraph of the Summary of the Invention thereof, relates to a double mutant yeast complemented with a plant channel gene. The only heterologous complementing gene described and enabled is the Arabidopsis plant gene.

Fairman et al. do not teach yeast mutants that are complemented by non-yeast genes. Moreover, Fairman et al. disclose a triple yeast potassium channel mutant which GROWS LESS WELL than the double mutant (page 153, right col., last para. through page 154, left col., first para.). Hence, as argued in the record, fastidious cells, such as the poorly growing triple mutant of Fairman et al., are difficult to grow, to maintain, and certainly are difficult to treat and to manipulate, such as, to expose that triple mutant cell to a harsh transformation procedure to accept and ultimately to express a transgene. If it were possible to get a heterologous gene into such a fragile yeast cell, there is no reasonable expectation of expressing such a human potassium channel, and then, there is no reasonable expectation to have that expressed human gene complement the triple mutant. The fragile state of the Fairman et al. cell would dissuade an artisan from having any interest in exposing that triple mutant to another genetic treatment

because of the poor likelihood of success. Finally, there is no basis to conclude that the resulting quadruple mutant could be used in a screening assay as claimed in the instant application with a reasonable expectation of success.

Thus, none of the relied on references, or any combination of the three references teaches or suggests obtaining yeast triple mutants that are complemented by a human channel gene with a reasonable expectation of success. Accordingly, a prima facie case of obviousness has not been made.

To reiterate, an objective of the present invention is to provide a method for the identification of substances which can modify the activity of a HUMAN potassium channel in a mutated yeast cell which does not express three endogenous potassium channels. At the priority date of the present invention, the artisan had the choice of using the expression system of either Pausch with only one deleted endogenous potassium channel with a cloned human potassium channel or of Gaber with two deleted endogenous potassium channels with a cloned PLANT potassium channel, i.e., a potassium channel of a totally different species from the human potassium channel of Pausch.

The use of the triple mutant as disclosed in Fairman et al. is not a reasonable choice at the priority date because: (a) Fairman et al. are silent on a potential use of the triple mutant in a screening assay for any potassium channel, even more for a human potassium channel, which would require expression of a human channel in that triple mutant, (b) the triple mutant grew less well than the double mutant (page, 153, right col., last sentence) and, therefore, there is no reasonable expectation that the triple mutant can be used successfully in the claimed screening process, and (c) "the role of TOK1 in wild-type yeast cells remains unclear and required further investigation." see Fairman et al., page 156, left column, last sentence.

Moreover, the inventors discovered that the human channels, HERG1 or Kv1.5, CANNOT complement the double mutant of Gaber (page 2, lines 11-12; and Example 5 of the instant specification). Consequently, the person skilled in the art would then be motivated to return to the expression system with the single mutant AND the human potassium channel as disclosed in Pausch. In view of the negative results obtained with the double mutant and two different human potassium channels, the skilled person would not have been motivated to use the

triple mutant described in Fairman et al., particularly with the above-specified problems (a)-(c) discussed above.

Surprisingly, the present inventors found that despite the inoperability of the double mutant of Gaber to be complemented by an introduced human potassium channel gene, the triple mutant as specified in currently pending claim 1 can be used IN COMBINATION WITH A HUMAN potassium channel. A human potassium channel is capable of FULLY complementing the growth deficiency of the triple mutant but not of the double mutant, as described in Example 5 of the present application. There was no reasonable expectation of success to obtain this surprising result in view of the teachings in the cited prior art.

The instant invention relates to the use of a human potassium channel expressed in a yeast triple mutant to identify modulators of that human potassium channel. None of the references or any combination of the references teaches using a human potassium channel in a triple mutant yeast in a screening assay. Moreover, there is no basis to conclude there is a reasonable expectation of successfully obtaining complementation of a triple mutant with a human potassium channel based on the teachings of the relied on references and the state of the art. Finally, the references themselves teach away from using a triple mutant, for example, Fairman et al. teaching the very sensitive nature of the triple mutant.

Hence, a prima facie case of obviousness has not been made and withdrawal of the rejection is in order.

III. On page 7 of the Office Action claim 4 was rejected under 35 U.S.C. 103(a) over Pausch in view of Gaber in view of Fairman and further in view of Rampe.

The rejection is traversed for the following reasons.

All of the arguments above as to Pausch, Gaber, and Fairman, and of record, are herein incorporated by reference in entirety.

Rampe et al. do not teach using yeast mutants as host cells, Rampe et al. used human channels in human cells. Thus, Rampe et al. do not teach or suggest expressing a human channel gene in a triple mutant yeast cell.

Therefore, Rampe et al. do not cure any of the fatal deficiencies of the three primary references as discussed above, Pausch, Gaber, and Fairman et al. Hence, a prima facie case of obviousness has not been made. Accordingly, the rejection can be removed.

CONCLUSION

Reexamination, reconsideration, withdrawal of the rejections and early notification of allowance are requested respectfully. If any questions remain, the Examiner is requested respectfully to contact the undersigned at the local exchange noted hereinbelow. The Director also hereby is authorized to charge Deposit Account No. 02-1818 for any additional fees required under 37 CFR 1.16 and 1.17 to maintain pendency of the instant application.

Respectfully submitted,

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